

WHAT IS CLAIMED IS:

1. A method of making an array comprising reversibly immobilized building blocks, the method comprising:
  - 5 forming a plurality of spots on a solid support, the spots comprising a plurality of building blocks;  
reversibly immobilizing building blocks on the solid support in the spots.
2. The method of claim 1, further comprising mixing the plurality of building  
10 blocks and employing the mixture in forming the plurality of spots.
3. The method of claim 1, wherein forming comprises piezoelectric spotting, pin spotting, electromagnetic spotting, or photolithography.
- 15 4. The method of claim 1, wherein the solid support comprises a glass plate or microscope slide.
5. A method of making a receptor surface, the method comprising:
  - 20 forming a region on a solid support, the region comprising a plurality of building blocks;  
reversibly immobilizing the plurality of building blocks on the solid support in the region.
6. The method of claim 5, further comprising mixing the plurality of building  
25 blocks and employing the mixture in forming the receptor surface.
7. The method of claim 5, wherein the solid support comprises a tube, plate, or well.
- 30 8. A method of making an artificial receptor, the method comprising:  
forming a region on a support, the region comprising a plurality of building blocks;

reversibly immobilizing building blocks on the support in the region.

9. The method of claim 8, wherein the region is a spot.

5 10. A composition comprising:  
a support, a functionalized lawn, and a plurality of building blocks;  
the functionalized lawn being coupled to the support;  
building blocks being reversibly immobilized on the lawn.

10 11. The composition of claim 10, wherein the functionalized lawn comprises a  
first covalent bonding moiety and the building block comprises a second covalent bonding  
moiety, the first and second covalent bonding moieties forming a readily reversible covalent  
bond.

15 12. The composition of claim 11, wherein:  
the first covalent bonding moiety comprises an amine nitrogen and the second  
covalent bonding moiety comprises a carbonyl carbon;  
the first covalent bonding moiety comprises a carbonyl carbon and the second  
covalent bonding moiety comprises an amine nitrogen;  
20 or combination thereof.

13. The composition of claim 10, wherein the functionalized lawn comprises a  
first charged moiety and the building block comprises a second charged moiety, the first and  
second charged moieties having opposite charges.

25 14. The composition of claim 13, wherein:  
the first charged moiety comprises a carboxylate and the second charged moiety  
comprises an ammonium;  
the first charged moiety comprises an ammonium and the second charged moiety  
30 comprises a carboxylate;  
or combination thereof.

15. The composition of claim 13, wherein the first charged moiety comprises amine, quaternary ammonium, sulfonium, phosphonium, ferrocene, or mixture thereof.

5 16. The composition of claim 13, wherein the second charged moiety comprises carboxylate, alkoxylate, phenol substituted with strongly electron withdrawing group, phosphate, phosphonate phosphinate, sulphate, sulphonates, thiocarboxylate, hydroxamic acid, or mixture thereof.

10 17. The composition of claim 10, wherein the functionalized lawn comprises a first lipophilic moiety and the building block comprises a second lipophilic moiety.

18. The composition of claim 17, wherein the first and second lipophilic moieties comprise independently branched or straight chain, substituted or unsubstituted C<sub>6-36</sub> alkyl; 15 branched or straight chain, substituted or unsubstituted C<sub>6-36</sub> alkenyl with 1 to 4 double bonds; branched or straight chain, substituted or unsubstituted C<sub>6-36</sub> alkynyl with 1 to 4 triple bonds; branched or straight chain, substituted or unsubstituted C<sub>6-36</sub> arylalkyl; branched or straight chain, substituted or unsubstituted C<sub>6-36</sub> arylalkenyl with 1 to 4 double bonds; branched or straight chain, substituted or unsubstituted C<sub>6-36</sub> arylalkynyl with 1 to 4 triple 20 bonds; polyaromatic hydrocarbon; substituted or unsubstituted cycloalkane; or mixtures thereof.

19. The composition of claim 17, wherein:  
the functionalized lawn comprises a first lipophilic moiety and a first covalent 25 bonding moiety; and the building block comprises a second lipophilic moiety and a second covalent bonding moiety;  
the functionalized lawn comprises a first lipophilic moiety and a first charged moiety; and the building block comprises a second lipophilic moiety and a second charged moiety; or combination thereof.

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20. The composition of claim 10, comprising a plurality of spots on the support, the spots comprising a plurality of building blocks.

21. The composition of claim 20, wherein the spots are configured in an array.

22. The composition of claim 21, wherein the array comprises more than 1 million spots.

23. The composition of claim 20, wherein the spots comprise 2, 3, 4, 5, or 6 building blocks.

24. The composition of claim 20, wherein the support comprises a solid support.

25. The composition of claim 24, comprising a plurality of spots on a surface of the solid support.

26. The composition of claim 24, comprising a functionalized glass support.

27. The composition of claim 10, comprising a candidate artificial receptor, a lead artificial receptor, a working artificial receptor, or a combination thereof.

28. The composition of claim 27, wherein the artificial receptor comprises 2, 3, 4, 5, or 6 different building blocks.

29. A heterogeneous building block array comprising:  
a support, a functionalized lawn, and a plurality of building blocks;  
the functionalized lawn being coupled to the support;  
a plurality of regions on the support;  
the regions comprising a plurality of building blocks; and  
building blocks being reversibly immobilized on the lawn.

30. A composition comprising:  
a surface, a functionalized lawn, and a plurality of building blocks;  
the functionalized lawn being coupled to the surface;  
a region on the surface comprising a plurality of building blocks;  
5 building blocks being reversibly immobilized on the lawn.
31. An article of manufacture comprising:  
a support, a functionalized lawn reagent, and a plurality of building blocks;  
the functionalized lawn being configured to be coupled to the support;  
10 the plurality of building blocks being configured to be reversibly coupled to the lawn.
32. The article of manufacture of claim 31, wherein the functionalized lawn  
reagent comprises a first covalent bonding moiety and the building block comprises a second  
covalent bonding moiety.  
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33. The article of manufacture of claim 31, wherein the functionalized lawn  
reagent comprises a first charged moiety and the building block comprises a second charged  
moiety, the first and second charged moieties having opposite charges.
- 20 34. The article of manufacture of claim 31, wherein the functionalized lawn  
reagent comprises a first lipophilic moiety and the building block comprises a second  
lipophilic moiety.
- 25 35. The article of manufacture of claim 31, comprising a functionalized glass  
support.
36. A method of using an artificial receptor comprising:  
contacting a reversibly immobilized heterogeneous molecular array with a test ligand;  
the array comprising:  
30 a support, a functionalized lawn, and a plurality of building blocks;  
the functionalized lawn being coupled to the support;

a plurality of regions on the support;  
the regions comprising a plurality of building blocks; and  
the plurality of building blocks being reversibly immobilized  
on the lawn;

5 shuffling building blocks in one or more regions;  
detecting binding of a test ligand to one or more regions; and  
selecting one or more of the binding regions as the artificial receptor;  
wherein the building blocks in the array define a first set of building blocks, and the  
plurality of building blocks in the one or more binding regions defines one or more selected  
10 binding combination of building blocks.

37. The method of claim 36, wherein the artificial receptor comprises a lead  
artificial receptor.

15 38. The method of claim 36, wherein:  
the functionalized lawn comprises a first covalent bonding moiety and the building  
block comprises a second covalent bonding moiety, the first and second covalent bonding  
moieties forming a readily reversible covalent bond; and  
shuffling comprises contacting one or more regions to be shuffled with a composition  
20 comprising reagent promoting cleavage of the readily reversible covalent bond;

39. The method of claim 36, wherein the readily reversible covalent bond  
comprises an acetal or ketal bond and the reagent comprises pH about 1 to about 4.

25 40. The method of claim 36, wherein:  
the functionalized lawn comprises a first charged moiety and the building block  
comprises a second charged moiety, the first and second charged moieties having opposite  
charges; and  
shuffling comprises contacting one or more regions to be shuffled with a composition  
30 comprising reagent promoting separation of the first and second charged moieties;

41. The method of claim 40, wherein the reagent comprises salt concentration of about 0.1 to about 1 M.

42. The method of claim 36, wherein:  
5 the functionalized lawn comprises a first lipophilic moiety and the building block comprises a second lipophilic moiety; and  
shuffling comprises contacting one or more regions to be shuffled with a composition comprising lipophilic reagent;

10 43. The method of claim 42, wherein the lipophilic reagent comprises organic solvent, surfactant, or mixture thereof.

44. The method of claim 42, wherein the organic solvent comprises acetonitrile, acetic acid, an alcohol, tetrahydrofuran (THF), dimethylformamide (DMF), hydrocarbon  
15 solvent, acetone, chloroform, methylene chloride, or mixture thereof.

45. The method of claim 36, comprising:  
shuffling before detecting;  
detecting before shuffling;  
20 shuffling, then detecting, then shuffling again;  
contacting, then shuffling, then contacting again; or  
combinations thereof.

46. The method of claim 36, further comprising  
25 determining the combinations of building blocks in one or more of the binding regions;  
developing, based on the combinations determined, one or more developed sets of building blocks distinct from those in the one or more selected combinations of building blocks;  
30 exchanging into one or more of the regions one or more of the developed sets of building blocks;

detecting binding of a test ligand to one or more of the exchanged regions; and  
selecting one or more of the spots of the second heterogeneous molecular array as the  
artificial receptor.

5           47.     The method of claim 46, wherein the artificial receptor comprises a lead  
artificial receptor.

48.     The method of claim 46, further comprising varying the structure of the lead  
artificial receptor to increase binding speed or binding affinity of the test ligand.

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49.     The method of claim 46, wherein the first set of building blocks comprises a  
subset of a larger set of building blocks.

50.     The method of claim 49, wherein the first set of building blocks comprises a  
15   subset of a larger set of building blocks, the second subset of building blocks defines a subset  
of the larger set of building blocks, and the first subset is not equivalent to the second subset.

51.     The method of claim 46, comprising:  
shuffling before detecting;  
20   detecting before shuffling;  
shuffling, then detecting, then shuffling again;  
contacting, then shuffling, then contacting again;  
exchanging before detecting;  
detecting before exchanging;  
25   exchanging, then detecting, then exchanging again;  
contacting, then exchanging, then contacting again;  
shuffling before exchanging;  
exchanging before shuffling; or  
combinations thereof.

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52. The method of claim 36, wherein the regions comprise 2, 3, or 4 building blocks.

53. The method of claim 36, further comprising:  
5 identifying the plurality of building blocks making up the artificial receptor;  
coupling the identified plurality of building blocks to a scaffold molecule;  
evaluating the scaffold artificial receptor for binding of the test ligand.

54. The method of claim 53, wherein:  
10 coupling comprises making a plurality of positional isomers of the building blocks on the scaffold;  
evaluating comprises comparing the plurality of the scaffold positional isomer artificial receptors; and  
selecting one or more of the scaffold positional isomer artificial receptors as lead or  
15 working artificial receptor.

55. The method of claim 36, further comprising applying the test ligand to one or more regions that function as controls for validating or evaluating binding to an artificial receptor.  
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56. The method of claim 53, wherein the control region comprises no building block, only a single building block, only functionalized lawn, or a combination thereof.

57. A method of using an artificial receptor comprising:  
25 contacting a first reversibly immobilized heterogeneous molecular array with a test ligand;

the array comprising:

a support, a functionalized lawn, and a plurality of building blocks;  
the functionalized lawn being coupled to the support;  
30 a plurality of regions on the support;  
the regions comprising a plurality of building blocks; and

the plurality of building blocks being reversibly immobilized  
on the lawn;  
exchanging building blocks onto or off of the support;  
detecting binding of a test ligand to one or more regions; and  
5 selecting one or more of the binding regions as the artificial receptor;  
wherein the building blocks in the array define a first set of building blocks, and the  
plurality of building blocks in the one or more binding regions defines one or more selected  
binding combination of building blocks.

10 58. The method of claim 57, wherein the artificial receptor comprises a lead  
artificial receptor.

59. The method of claim 57, wherein exchanging comprises contacting one or  
more regions with added building block and reversibly immobilizing the added building  
15 block in the region.

60. The method of claim 57, wherein exchanging comprises contacting one or  
more regions with reagent promoting release of reversibly immobilized building block and  
removing released building block.

20 61. The method of claim 57, wherein exchanging comprises:  
contacting one or more regions with reagent promoting release of reversibly  
immobilized building block and removing released building block; and  
contacting one or more regions with added building block and reversibly  
25 immobilizing the added building block in the region.

62. The method of claim 57, further comprising shuffling building blocks in one  
or more regions.

30 63. The method of claim 62, comprising:  
shuffling before detecting;

detecting before shuffling;  
shuffling, then detecting, then shuffling again;  
contacting, then shuffling, then contacting again;  
exchanging before detecting;  
5 detecting before exchanging;  
exchanging, then detecting, then exchanging again;  
contacting, then exchanging, then contacting again; or  
shuffling before exchanging;  
exchanging before shuffling; or  
10 combinations thereof.

64. The method of claim 57, comprising:  
exchanging before detecting;  
detecting before exchanging;  
15 exchanging, then detecting, then exchanging again;  
contacting, then exchanging, then contacting again; or  
combinations thereof.

65. The method of claim 57, further comprising  
20 determining the combinations of building blocks in the one or more binding regions;  
developing, based on the combinations determined, one or more developed sets of  
building blocks distinct from those in the one or more selected combinations of building  
blocks;  
exchanging into one or more of the regions the one or more developed sets of  
25 building blocks;  
detecting binding of a test ligand to one or more of the exchanged regions; and  
selecting one or more of the regions of the second heterogeneous molecular array as  
the artificial receptor.

30 66. The method of claim 65, wherein the artificial receptor comprises a lead  
artificial receptor.